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EXAMINER	
DOWELL, PAUL THOMAS	

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,670	LI ET AL.	
	Examiner	Art Unit	
	Paul Dowell	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9 and 11-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/8/04,1/26/05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *3/29/2006* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-6, drawn to ONE colon cancer transcriptional regulatory element (TRE) sequence, classified in class 536, subclass 23.1.

(Upon election of Group I, applicant must further choose ONE nucleic acid SEQ ID NO. from Claims 4 and 5: as each nucleotide sequence represents an independent invention, not a species.)

II. Claims 7-21, drawn to a replication-competent adenovirus vector comprising an adenovirus gene essential for replication under transcriptional control of ONE metastatic colon cancer cell specific TRE, classified in class 424, subclass 93.6.

(Upon election of Group II, applicant must further choose ONE nucleic acid SEQ ID NO. from Claims 9 and 10 (i.e. either SEQ ID NO:1 or SEQ ID NO:2): as each nucleotide sequence represents an independent invention, not a species.)

The inventions are distinct, each from the other because of the following reasons:

Inventions of Group I and Group II are directed to related products. The related inventions are distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive; the inventions as claimed are not obvious variants; and the

inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j). In the instant case, Group I is related to Group II in that the Group II is drawn to a replication-competent adenovirus vector, which comprises the TRE claimed in Group I. However, the Groups are distinct. The TRE could be used in a process other than controlling the adenovirus gene expression. For example, the TRE could be used to control expression of other non-adenoviral genes, such as luciferase, for the monitoring of gene activity in reporter gene assays. Further, the replication-competent adenovirus vector of Group II can be used to infect a host cell while the TRE of Group I cannot be used as such. The inventions of Groups I and II do not overlap in scope because each is drawn to structurally and functionally distinct products (i.e. Group I is drawn to a nucleic acid TRE while group II is drawn to an adenovirus vector). The inventions of Groups I and II are not obvious variants because it is unpredictable whether nucleic acid regulatory elements (e.g. the TRE of Group I) are functional when incorporated into adenoviral vectors (e.g. the adenovirus vector of Group II). The art of record at the time of the invention recognized the unpredictable nature of tumor-specific promoters when incorporated into viral vectors. For example, Alemany et al **(Nature Biotechnology, 18:723-727, 2000)** teaches the state of the art of conditionally replicative adenoviruses for therapeutic treatment of cancers. Alemany teaches that "the predicted replication selectivity has not been realized because of incomplete knowledge of the complex virus-cell interactions and the leakiness of cellular promoters in the viral genome" (Abstract, lines 8-10). Alemany teaches that: "transcription of viral genes has been

controlled by replacing native viral promoters with tumor-specific promoters" (page 724, col. 1, paragr. 2, lines 6-7); "nonetheless, we have learnt that, in reality, achieving tumor-selective replication is not so simple" (page 724, col. 1, paragr. 2, lines 14-15); "it is known that cellular promoters do not keep the proper fidelity in the viral genome" (page 725, col. 1, paragr. 1, lines 9-10); and "low levels of viral products such as E1a may be sufficient for replication, thus preventing specificity" (page 725, col. 1, paragr. 1, lines 10-11).

Furthermore, searching all of the claims (i.e., both Groups) would invoke a burdensome search because the inventions have been classified separately. Thus, each invention has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search. This would necessitate different searches in the patent and or non-patent literature and the consideration of different patentability issues. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Furthermore, because these inventions are distinct for the reasons given above and the search required for one group is not required for another group, restriction for examination purposes as indicated is proper.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Telephonic Election

During a telephone conversation with Ms. Linda Judge (tel: 415-836-2586) on 3/29/2006 a provisional election was made with traverse to prosecute the invention of group II, claims 7-21 and election of SEQ ID NO:1. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-6 and 10 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 7-9 and 11-21 are under examination in the instant office action.

Priority

Applicant's claim for the benefit of a U.S. Provisional Application No. 60/397,859 ('859) is acknowledged. It is noted that Example 3 of the instant specification (page 31, paragrs. 115-117) is not disclosed in '859. It is also noted that Fig. 2 of the drawings of the instant specification is not identical to Fig. 2 of the drawings of '859.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7, 11-19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-41 of **U.S. Patent No. 6,692,736** ('736). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-41 of '736 are drawn to a replication-competent adenovirus vector comprising at least one adenoviral gene that is essential for viral replication (claim 4), wherein said adenoviral gene is E1A and/or E1B (claim 11), wherein the E1B has a deletion of the 19-kDa region (claim 15), wherein said adenoviral gene is under transcriptional control of a heterologous target cell-specific transcriptional regulatory element, wherein said TRE is specific for a target cell that is a cancer cell (claim 22), wherein said cancer cell includes a colon cancer cell (claim 23). As such, claims 7, 11-19 of the instant application are entirely encompassed by claims 1-41 of '736.

Drawings

The drawings are objected to under 37 CFR 1.83(a) because they fail to show the results with the cell line termed "Colo 201" as described in the specification on page 30, paragr. 113. Specifically, the specification refers to "Colo 201" while the results represented in Fig. 2 refers to "Col 201". It is not clear if the specification and the instant drawing are referring to the same cell line. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claims 8 and 20 are objected to because of the following informalities: claims 8, 10 and 20 are drawn to a non-elected invention. Specifically:

Claim 8 depends from claim 5; however, claim 5 has been withdrawn as being drawn to a non-elected invention. It is noted that claim 8 is interpreted to depend from claim 7.

Claim 20 recites, "a replication-competent adenovirus vector according to claim 6; claim 6 has been withdrawn as being drawn to a non-elected invention. It is noted that claim 20 is interpreted to depend from claim 7.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 21 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The term "host cell" as defined by the instant specification at page 16, paragr. 64 states that a "host cell" includes an individual cell or cell culture which can be or has been a recipient of an adenoviral vector(s) of this invention". As such, the scope of the instant claim encompasses an individual cell within a human being, said individual cell being a recipient of an adenoviral vector. As said individual cell can be integrated into a human being, said individual cell is considered an inseparable part of a human being and human beings are considered non-statutory subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 7-9 and 11-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make

or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The instant claims are drawn to an adenovirus vector comprising an adenovirus gene essential for replication under transcriptional control of a metastatic colon cancer cell specific transcriptional regulatory element (TRE; claims 7-9 and 11-19), a composition comprising said adenovirus vector and a pharmaceutically acceptable excipient (claim 20) and a host cell comprising said adenovirus (claim 21).

The specification discloses a general background of the PRL-3 gene, colorectal cancer, oncolytic adenoviral vectors and methods of treating cancer by administering said adenoviral vectors. The specification discloses three working examples (page 30, paragr. 112 to page 31, paragr. 117). Example 1 discloses cloning of putative human PRL-3 gene regulatory regions including a 0.6 kb DNA fragment located 5' to the PRL-3 gene coding sequence as set forth in SEQ ID NO:1. Example 2 discloses that plasmids comprising the nucleic acid of SEQ ID NO:1, when said nucleic acid is operably linked to a luciferase reporter gene and when transiently transfected into a panel of cancer cell lines, promoted "specific activity in metastatic colon cell lines". Example 3 discloses that plasmids comprising the nucleic acid encompassing "an extended 1 kb DNA fragment

from the PRL-3 TRE region" (presumably represented by SEQ ID NO:2), when said nucleic acid is operably linked to a luciferase reporter gene and when transiently transfected into LoVo and SW620 colon cancer cell lines, promoted expression of the operably linked luciferase gene.

However, the specification discloses in Example 2 that the nucleic acid of SEQ ID NO:1 is not a metastatic colon cancer cell specific transcriptional regulatory element. The specification defines a "metastatic colon cancer-specific transcriptional response element" as an element that "preferentially directs gene expression in metastatic colon cancer cells" (page 7, paragr. 30). The results presented in Fig. 2 demonstrate that the nucleic acid of SEQ ID NO:1 drives expression of an operably linked luciferase reporter gene in Panc-1, LNCap and Hep3B cells representing pancreatic, prostatic and hepatic cancer cell lines, respectively. Further, the specification discloses that PRL-3 is expressed in normal muscle and heart tissues in humans (page 1, paragr. 04) and Saha et al **(Science, 294:1343-1346, 2001, IDS)** confirms that "among normal human tissues, it [PRL-3] is expressed predominantly in muscle and heart" (page 1344, col. 2, lines 4-5). Thus, the results disclosed in the specification demonstrate that the nucleic acid of SEQ ID NO:1, representing a fragment of the regulatory region of the PRL-3 gene, does not appear to drive expression of operably linked nucleic acids preferentially in metastatic colon cancer cells and the art of record at the time of the invention suggests that regulatory regions within the PRL-3 gene are capable of directing expression in muscle and heart. Further, it is not clear from the art of record at the time of the invention that transcriptional regulatory regions of the PRL-3 gene were capable of

directing metastatic colon cancer cell-specific expression. For example, Saha teaches that PRL-3 is overexpressed in human metastatic colon cancer biopsies but Saha does not teach any regulatory regions of the PRL-3 gene that are responsible for colon cancer cell-specific expression. In contrast, Saha provides evidence that PRL-3 overexpression in said biopsies may be the result of gene amplification of the PRL-3 gene (i.e. increased copy number of PRL-3 genes) and not necessarily a result of increased transcriptional activation of individual PRL-3 genes (page 1345, col. 3, lines 3-7). Thus, neither the specification nor the art of record at the time of the invention provide enabling support to allow an artisan to make an adenoviral vector or any vector comprising a metastatic colon cancer-cell specific transcriptional regulatory element, particularly when said regulatory element comprises regulatory regions of the PRL-3 gene.

The breadth of claims 7, 8, 11-21 is such that they read on adenoviral vectors comprising TREs of any size and thus, encompass adenoviral vectors comprising nucleic acid of any size. The art of record at the time of the invention teaches that adenoviral vectors have well established upper and lower size limitations regarding the amount of DNA that can be packed within said vectors. For example, Parks et al **(Journal of Virology, 71:3293-3298, 1997)** teaches that:

> "Adenoviruses (Ads) are intermediate-sized mammalian DNA viruses with a double-stranded linear genome of 36 kb. The icosohedral virion has been shown to accommodate up to 105% of the wild-type genome length, and genomes larger than this size are either unpackageable or extremely unstable, frequently undergoing DNA rearrangement. Here we show that the Ad virion also has a lower packaging limit of approximately 75% of the wild-type genome length." (Abstract, lines 1-5)

The specification does not provide specific guidance or working examples to allow an artisan to make the claimed adenoviral vectors comprising nucleic acid of any size and therefore an artisan would experience undue experimentation to make the claimed invention.

Further, claim 20 is drawn to a composition comprising said adenovirus vector and a pharmaceutically acceptable excipient and as such, claim 20, given broadest reasonable interpretation, is drawn to a pharmaceutical composition. It is noted that: "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c). When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. With respect to the claim breadth, the standard under 35 U.S.C. § 112, first paragraph entails the determination of what the claims recite and what the claims mean ***as a whole***. "A composition comprising an adenoviral vector and a pharmaceutically acceptable excipient", for example, is defined as a composition with an intended therapeutic use (i.e. to prevent, diagnose, alleviate, treat or cure a disease to which said composition is administered) and, therefore, will be evaluated by the standard. As such, the broadest reasonable interpretation of the claimed invention properly encompasses a replication-competent adenovirus vector for treatment of cancer and specifically, for treatment of colorectal cancer.

The specification contemplates an intended use of the claimed products for treatment (for example, page 4, paragr. 18 to page 5, paragr. 19; page 26, paragr. 96 to page 30, paragr. 110). However, the specification does not disclose that the claimed adenovirus vectors were either constructed or tested, either *in vitro* or *in vivo*. The art of record at the time of the invention recognized the unpredictable nature of tumor-specific promoters when incorporated into viral vectors. For example, Alemany et al **(Nature Biotechnology, 18:723-727, 2000)** teaches the state of the art of conditionally replicative adenoviruses for therapeutic treatment of cancers. Alemany teaches that "the predicted replication selectivity has not been realized because of incomplete knowledge of the complex virus-cell interactions and the leakiness of cellular promoters in the viral genome" (Abstract, lines 8-10). Alemany teaches that: "transcription of viral genes has been controlled by replacing native viral promoters with tumor-specific promoters" (page 724, col. 1, paragr. 2, lines 6-7); "nonetheless, we have learnt that, in reality, achieving tumor-selective replication is not so simple" (page 724, col. 1, paragr. 2, lines 14-15); "it is known that cellular promoters do not keep the proper fidelity in the viral genome" (page 725, col. 1, paragr. 1, lines 9-10); and "low levels of viral products such as E1a may be sufficient for replication, thus preventing specificity" (page 725, col. 1, paragr. 1, lines 10-11).

The specification discloses only results of PRL-3 promoter-luciferase reporter assays where circular plasmids comprising PRL-3 promoter regions were analyzed. Babiss et al **(Molecular and Cellular Biology, 6:3798-3806, 1986, IDS)** teaches that at

the time of the invention it was known that cellular promoters, when incorporated into adenoviral vectors, exhibited unpredictable activity. Specifically, Babiss teaches that:

> "The activities of transcription factors (either positive or negative) are very likely different when promoters are on circular plasmids than with a linear adenovirus template. Which presents a more valid picture of how sequences in their native chromosomal locus are regulated is not clear." (page 3805: col. 1, paragr. 3, line 5 to col. 2, line 2)

As such, the state of the art at the time of the invention teaches that the activity of cellular promoters, when transferred to viral genomes, is unpredictable and the specification provides no guidance to address such unpredictability.

Further, the art of record at the time of the invention teaches that tumor lines in culture are not always a faithful representation of tumors *in situ*. For example, Zhang et al **(Science, 276:1268-1272, 1997)** provides the following teachings when comparing tumor cell lines with tumors *in situ*:

> "The fact that many, but not all, of the differences were preserved during in vitro culture demonstrates the utility of cultured lines for examination of some aspects of gene expression but also provides a note of caution about relying on such lines to perfectly mimic tumors in their natural environment" (page 1271: col. 2, paragr. 1, last three lines to col. 3, line 5).

Thus, even if the specification had disclosed *in vitro* testing of the claimed adenoviral vectors on specific tumor cell lines, the art of record at the time of the invention teaches that translation of such results into *in vivo settings* is unpredictable.

Still further, the art of record at the time of the invention recognized the unpredictability of using adenoviral vectors for cancer therapy. Henderson et al **(Monographs in Virology, Eds. Driever PH and Rabkin SD (Basel, Karger), 22:57-80, 2001, IDS)** teaches that while promising, treatment of cancers with conditionally

replicative adenoviral vectors was unpredictable and not routine at the time of the invention. For example, Henderson teaches that massive doses of adenovirus will be required to effect treatment and that "very little is known about the human host reponse to large doses of adenoviruses and nothing is known about the human host response to using the intravenous route of administration of large doses of replicating adenoviruses. Liver toxicity of virion proteins may be limiting at these high doses." (page 74, paragr. 3, line 1 to page 75, line 6). Henderson also teaches the many hurdles that a systemically delivered replicating adenovirus is going to face including "the nonspecific removal of adenovirus by liver Kupffer cells, the inactivation of virus by pre-existing circulating antibodies to adenovirus, a limitation of viral replication mediated by a vigorous CTL response to virally infected cells and a limitation of the efficacy of repeat dosage by primary or secondary induction of humoral immunity" (page 75, paragr. 1). Thus, at the time of the invention, treatment of cancers with conditionally replicative adenovirus was not routine and was unpredictable.

Chen et al **(BioDrugs, 15:357-367, 2001)** teaches the state of the art of gene therapy for colorectal cancer at the time of the invention including oncolytic adenoviruses. Chen recites, "Although the preclinical results of gene therapy for colorectal cancer have been promising, clinically significant antitumoural efficacy has still to be proven" (page 365, col. 2, paragr. 1, lines 1-4); "Gene therapy for colorectal cancer is still in its infancy. Before it can be applied in standard clinical practice, several significant hurdles need to be overcome" (page 364, col. 2, paragr. 2). Thus, at the time

of the invention, gene therapy for colorectal cancer at the time of the invention, including oncolytic adenoviruses, was not routine and was unpredictable.

In summary, an artisan of skill would have required extensive experimentation to make and use the claimed invention. Such experimentation will be undue because of the unpredictability of metastatic colon cancer specific transcriptional regulatory elements, the unpredictability of transcriptional regulatory elements within the PRL-3 gene, the unpredictability of packaging a viral genome of any size within an adenoviral vector, the unpredictability of cellular promoters to direct tissue- or tumor-specific expression of operably linked nucleic acids when said cellular promoters are incorporated into a viral genome, the unpredictability of cultured tumor cell lines as faithful model of tumors *in situ* and the unpredictability of oncolytic viruses as therapeutic agents in treating cancer in general, and specifically, in treating colon cancer. Neither the specification nor the art of record at the time of the invention provides sufficient guidance to address these issues for an artisan to make and use the claimed invention.

Written Description

Claims 7-9 and 11-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to an adenovirus vector comprising an adenovirus gene essential for replication under transcriptional control of a metastatic colon cancer cell specific TRE (claims 7-9 and 11-19), a composition comprising said adenovirus vector and a pharmaceutically acceptable excipient (claim 20) and a host cell comprising said adenovirus (claim 21). Claim 8 further limits said TRE to comprising a sequence derived from the sequence 5' to the translational start codon of the PRL-3 gene. Claim 9 further limits said TRE to being derived from the 0.6 kb sequence upstream of the translational start codon for the PRL-3 gene, presented in the instant specification as SEQ ID NO:1.

The specification has defined the term "metastatic colon cancer-specific transcriptional response elemet" as being a TRE that preferentially directs gene expression in metastatic colon cancer cells (page 7, paragr. 30). Furthermore, TRE is defined as a polynucleotide sequence, preferably a DNA sequence, comprising one or more enhancers and/or promoters and/or promoter elements such as a transcriptional regulatory protein response sequence in a host cell that allows that TRE to function (page 7, paragr. 30). The specification is silent with respect to a definition of what is intended by the term "derived from", as recited in claim 9, and therefore it is interpreted in the broadest reasonable terms to mean variants including deletions, substitutions and insertions of the disclosed sequence. Claim 7 is a generic claim in terms of an adenoviral vector comprising a nucleic acid having any structure which is a metastatic colon cancer cell specific TRE. As such, said claim encompasses a broad class of products that are defined by function only. The disclosure is not descriptive of the

complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the products encompassed by the claim based on the teachings of the specification. The specification provides information on the structure of two TRE polynucleotides (i.e. SEQ ID NO:1 and SEQ ID NO:2) which are disclosed as being specific for metastatic colon cancer cells, however, there is no structure-function analysis of the disclosed TRE to provide guidance on the essential nucleotides or structure of the molecule which could be modified and still retain function. Therefore, the specification does not describe the claimed products so as to indicate that Applicants had possession of the products claimed at the time of filing the instant application. Thus, the written description requirement has not been satisfied.

Further, claims 8 and 9 are genus claims in terms of adenoviral vectors comprising a nucleic acid having any variant structure including fragments, which is a TRE that has been derived from the sequence of a PRL-3 gene or the sequence disclosed as SEQ ID NO:1. The instant claims encompass a broad class of products that are defined by function, that is they act as a TRE and are specific for metastatic colon cancer cells. The disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the products encompassed by the claims based on the teachings of the specification. While the specification provides information on the structure of the TRE which is represented by SEQ ID NO:1 and SEQ ID NO:2, there is no structure-function analysis of the disclosed TREs to provide guidance on the essential nucleotides or structure of the molecule which could be modified and still

retain function. There are not teachings in the prior art regarding the elements that are responsible for the specific activity of a TRE in metastatic colon cancer cells that would provide guidance on which fragments of the polynucleotide shown in SEQ ID NO:1 would still retain activity, or which residues could be modified and still retain activity. Thus, the written description requirement has not been met.

Claims 11-21 depend from claims 7, 8 and/or 9 and therefore are likewise rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Further, Applicant's attention is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In conclusion, Applicant's disclosure of two species (i.e. SEQ ID NO:1 and SEQ ID NO:2) of the claimed broad genus is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the claimed broad genus at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-9 and 11-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "specific" recited in claims 7-9 and 11-15 is a relative term which renders the claims indefinite. The term "specific" is not defined by the claim. Further, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification recites: "[A] metastatic colon cancer-specific transcriptional response element ***preferentially*** directs gene expression in metastatic colon cancer cells" (page 7, paragr. 30, emphasis added) and "[A] TRE is determined to be cell-specific if it is ***preferentially*** functional in one cell type, compared to a different cell type" (page 9, last sentence of paragr. 36, emphasis added). The terms "specific" and "preferentially" are both relative terms. Claims 16-21 depend directly or indirectly from claims 7-9 and 11-15 and are likewise rejected.

Claim 8 recites, "the adenovirus vector according to claim 5"; however, claim 5 does not recite any adenovirus vector. There is insufficient antecedent basis for this limitation in the claim. Claim 9 depends from claim 8 and is likewise rejected.

Claim 19 recites, "the adenovirus vector of claim 16, wherein E1B has..."; however, claim 16 does not recite any E1B nor does any claim from which claim 16 depends recite any E1B.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7, 11 and 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hallenbeck et al **(U.S. Patent 5,998,205, IDS)**.

Hallenbeck teaches adenoviral vectors for tissue-specific replication and oncolytic activity in cancers. Hallenbeck teaches a human colon cancer CEA-specific promoter that is operably linked to an adenoviral gene which is essential for replication (e.g. E1A and E1B) (col. 4, lines 2-14; col. 5 lines 62-63; col. 6 lines 10-12; col. 13, lines 11-18; col. 22, lines 32-38;).

Conclusions

No claims are allowed.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment and provide any statements that might help to identify support for the claimed invention (e.g. if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Dowell whose telephone number is 571-272-5540. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER